REMARKS

Claims 1-16 are pending in the application. Claims 1-2, 4-8, 11-13 and 15 have been amended. Claims 3 and 17-22 have been cancelled.

Claim Amendments

Claim 1 has been amended to recite "to form at least one encapsulant." Support for this amendment can be found at least in the Specification at p.6, paragraph [0021], as well as in originally filed claim 1.

Claims 1-2, 4-6 and 8 have been amended to recite "PEO-based block copolymer" Support for this amendment can be found at least in the Specification at Abstract, at p.20-21, paragraphs [0072-0077], as well as in originally filed claim 1.

Claim 1 has been amended to recite "polyester." Support for this amendment can be found at least in the Specification at p. 7, paragraph [0025], p. 8, paragraph [0027], p.47, paragraph [175], as well as originally filed claims 1 and 4.

Claim 1 has been amended to recite "inert." Support for this amendment can be found at least in the Specification at p.48, paragraph [0176], as well as originally filed claim 1.

Claim 1 has been amended to recite "having at least one hydrophobic component." Support for this amendment can be found at least in the Specification at Abstract, at p.7, paragraph [0026], p.15, paragraph [0053], as well as originally filed claim 1.

Claim 1 has been amended to recite "based upon the blend ratio." Support for this amendment can be found at least in the Specification at Abstract, at page 8, paragraph 27 and at page 58, paragraph 208.

Claim 1 has been amended to recite "without the use of a co-solvent." Support for this amendment can be found at least in the Specification at page 28, paragraph 0103.

No new matter has been added by way of these amendments.

Rejection under 35 U.S.C. 112 (First Paragraph)

Claims 1-16 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner asserts that claim 1,

amended to recite "without secondary chemical processing," enters new matter into the claims, and that the originally filed disclosure does not disclose secondary chemical processing, either as a positive or negative recitiation. The remaining claims are rejected as ultimately depending on claim 1.

Applicants respectfully submit this language, while not introducing new matter, has been removed, and claim 1 has been amended again to more accurately reflect that which is disclosed in the Specification of the present application. Specifically, claim 1 has been amended to recite, in part:

> blending in aqueous solution the hydrolysable PEO-based block copolymer together with the at least one inert PEO-based block copolymer to effect self-assembly of the amphiphilic PEO-based polymersomes, ***without the use of a co-solvent...***
>
> (emphasis added)

Support for this amendment can be found in the Specification at page 28, paragraph 0103, which reads:

> The disclosed methods of preparation of the polymersomes are particularly preferred because the vesicles are prepared without the use of co-solvent. Any organic solvent used during the disclosed synthesis or film fabrication method has been completely removed before the actual vesicle formation. Therefore, the polymersomes of the present invention are free of organic solvents, distinguishing the vesicles from those of the prior art and making them uniquely suited for bio-applications.

In light of the present amendments and arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-16 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. 112 (Second Paragraph)

Claims 1-16 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention.

Specifically, Claim 1 recites "secondary chemical processing", which the Examiner asserts is not clear. Applicants respectfully submit claim 1 has been amended to remove this language, rendering this rejection moot.

Further, the Examiner asserts that claim 1 is also unclear wherein it recites "determining the appropriate blend ratio (mol %) of hydrolysable PEO-block copolymer of at least one hydrophilic component and at least one more hydrophobic PEO-block copolymer component." Applicants respectfully submit that claim 1 has been amended to clarify this element as "determining the appropriate blend ratio (mol %) of a hydrolysable PEO-based block copolymer having at least one polyester component, and at least one inert PEO-based block copolymer having at least one hydrophobic component..." This amendment clarifies that there are two different PEO-based block copolymers being blended, the first being a hydrolysable PEO-based block copolymer having at least one polyester component, and the second being at least one inert PEO-based block copolymer having at least one hydrophobic component.

Further still, the Examiner asserts that claim 1 is also unclear wherein it recites "hydrophobic block copolymer to effect controlled polyester chain hydrolysis in the membrane.", and "hydrophilic PEO." Applicants respectfully submit that claim 1 has been amended to clarify these elements. Claims 3, 5-8, 11-13 and 15 were also amended to clarify similar elements.

In light of the present amendments and arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-16 under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. 103(a)

Claims 1-16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Piskin et al. (J Biomater. Sci. Polymer Edn., 1995), in view of Won et al., (Science, 1999). The Examiner asserts that Piskin teaches a method of using copolymer made from PEG-PLA (referred to as PEG/PDLLA in the article) to form micelles; that the polymers are used to encapsulate doxorubicin; and that the release of the drug is controlled by degradation of the PLA component of the micelles. The Examiner also asserts that Won teaches that PEG-PBD can be used to form micelles. Notably, the Examiner admits that any teaching of blending the PEG-PLA with PEG-PBD to form micelles is lacking. However, the Examiner asserts it would

have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to form a micelle from a mixture of PEG-PBD and PEG-PLA.

Applicants respectfully disagree. For at least the following reasons, the cited references, either separately or in any combination, do not teach or suggest each of the limitations of amended claim 1.

According to the U.S. Supreme Court ruling in *Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966)*, in making a *prima facie* case for obviousness, the Examiner must 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. These principles have been reconfirmed by the Supreme Court in *KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007).*

To establish a prima facie case of obviousness, all the claim limitations must be taught or suggested by the prior art. See *In re Royka, 490 F.2d 981, 985, 180 USPQ 580 (CCPA 1974).* In determining the differences between the prior art and the claims under the Graham analysis, the invention as a whole must be considered (MPEP 2141.02; citing *Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)*; *Schenck v. Nortron Corp., 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983)*. Furthermore, objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. See *Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966)*. "Secondary considerations" may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results.

Applicants respectfully submit that neither Piskin nor Won, either separately or in combination, teach or suggest a method of vesicle formation where the release rate of the encapsulated encapsulant is based upon the blend ratio of a hydrolysable PEO-based block copolymer having at least one polyester component, and at least one inert PEO-based block copolymer having at least one hydrophobic component. Piskin teaches only a micelle composed of PDLLA/PEG copolymers. Won teaches only a micelle composed of hydrophobic copolymers. Therefore, not only is each reference missing the other copolymer type, but they are both missing any blend ratio that determines the release rate of the encapsulant. In fact, it is impossible for either reference to teach such a blend ratio, simply because the micelles of both Piskin and Won are not blends of the claimed copolymer types. The release rates for the micelles of either Piskin or Won are based only on the inherent breakdown of their degradable

copolymer components. This is entirely different from the claimed invention, which uses the blend ratio of both copolymer types to uniquely customize and determine the release rate of the formed vesicle. This is a property unique to the claimed invention, and is entirely absent in the cited references of Piskin and Won.

Additionally, Applicants respectfully submit that Piskin does not teach a method of vesicle formation comprising blending in aqueous solution the hydrolysable PEO-based block copolymer together with the at least one inert PEO-based block copolymer to effect self-assembly of the amphiphilic PEO-based polymersomes, without the use of a co-solvent, as recited in amended claim 1. In contrast, Piskin teaches micelle formation of PDLLA/PEG copolymers using a process called transesterification. As transesterification necessarily requires exchanging the alcohol group of an ester compound with another alcohol, a co-solvent must be present during the formation of the micelle as taught by Piskin. In fact, Piskin first teaches the use of acetone as the co-solvent, followed by exposure to nitrogen gas during transesterification (See Piskin at p.361, line 32 to p.362, line 5).

The Examiner also asserts that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. Further still, it is asserted that because PEG-PLA and PEG-PBD are both known to make micelles, it would purportedly follow that a method of forming micelles by mixing two components known to form micelles constitutes prime facie obvious subject matter. Lastly, the Examiner asserts that the record does not indicate any unexpected result stemming from the combination.

Applicants strongly, but respectfully disagree. Not only are Piskin and Won silent as to any suggestion to combine their specific respective copolymers, they are silent as to combining their respective copolymers with any other copolymer type. Furthermore, the skilled artisan would simply not be motivated to combine the copolymers of Piskin and Won, as the vesicles formed by each of these copolymers separately are drastically structurally different. The resulting micelles formed by Piskin are classically sized micelles, with densities varying based on PEG content. In contrast, the resulting micelles formed by Won are giant, wormlike rubber micelles that are actually macro-molecules with molar masses more than three orders of magnitude greater than those typical of large conventional synthetic polymers. Further, these

giant, wormlike rubber micelles exhibit unusual viscoelastic properties not found in the micelles taught by Piskin (See Won at p.960).

Applicant also respectfully submits that there is certainly a valuable and unexpected result from the blending of copolymers, as recited in claim 1. The purpose of determining the blending ratio of the different copolymers, and subsequently blending them at this ratio is to create a vesicle having the unique property of a specificly designed release rate of the encapsulated active agent. In other words, the determined blending ratio effectuates a unique vesicle with a customizable release rate that is very different from the release rate of a vesicle formed by either one of the copolymers individually. This ability to effectively control the release rate of the resulting vesicle by blending the two copolymer types ***is an unexpected property not found in the teachings of Piskin or Won***. Consequently, this blend-dependent release rate is an unexpected result and goes to the heart of the claimed invention. As explained by Applicants, rates of release of an encapsulant rise linearly with the molar ratio of a non-degradable, PEG-based copolymer like PEG-PBD (See Specification at p.7, paragraph 0026). It should be readily apparent to one skilled in the art that you simply cannot expect or anticipate the resulting control of vesicular release rates simply by creating vesicles of the individual copolymers.

In light of the present amendments and arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-16 under 35 U.S.C. § 103(a).

CONCLUSION

Wherefore, Applicants believe that all outstanding grounds raised by the Examiner in the present Office Action have been addressed, and respectfully submit the present case is in condition for allowance, early notification of which is earnestly solicited. Should there be any questions or outstanding matters, the Examiner is cordially invited and requested to contact Applicants' undersigned attorney at his number listed below.

Respectfully submitted,
DENNIS E. DISCHER, *ET AL.*

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Date

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